09/016,869

Trying 9351006...Open

Welcome to STN International! Enter x:x
LOGINID:ssspta1816mxt
PASSWORD:
TERMINAL (ENTER 1, 2, 3, OR ?):2

********** Welcome to STN International **********

NEWS 1 Feb 2 Web Page URLs for STN Seminar Schedule - N. America
NEWS 2 Jul 8 Important Derwent Announcement about CPI Changes to CPI Subscriber Indexing in 1999 - REVISED
NEWS 3 Aug 2 New INPADOC File Now Available on STN
NEWS 4 Aug 9 Expanded CAplus Coverage of US, Japanese and WIPO Patents
NEWS 5 Aug 23 Left Truncation Added to Several STN Files
NEWS 6 Aug 30 The International Patent Classification in English and German available on STN
NEWS 7 Aug 30 IFIRXA File has changed to IFICLS
NEWS 8 Aug 30 IMSworld Pharmaceutical Company Profiles (IMSPROFILES) from IMS HEALTH now on STN
NEWS 9 Sep 1 IFIPAT Pricing Changes
NEWS 10 Sep 7 ESBIOBASE - Elsevier Biobase now on STN

NEWS EXPRESS STN Express 5.0 Now Available
NEWS HOURS STN Operating Hours Plus Help Desk Availability
NEWS INTER General Internet Information
NEWS LOGIN Welcome Banner and News Items
NEWS PHONE Direct Dial and Telecommunication Network Access to STN
NEWS WWW CAS World Wide Web Site (general information)

Enter NEWS followed by the item number or name to see news on that specific topic.

All use of STN is subject to the provisions of the STN Customer agreement. Please note that this agreement limits use to scientific research. Use for software development or design or implementation of commercial gateways or other similar uses is prohibited and may result in loss of user privileges and other penalties.

********** STN Columbus **********

FILE 'HOME' ENTERED AT 11:14:07 ON 17 SEP 1999

=> s (ccr or cell cycle regulatory) and (cdk or cyclin dependent kinase) and (antibod? or monoclon? or ccr binding)

THIS COMMAND NOT AVAILABLE IN THE CURRENT FILE
Some commands only work in certain files. For example, the EXPAND command can only be used to look at the index in a file which has an index. Enter "HELP COMMANDS" at an arrow prompt (=>) for a list of commands which can be used in this file.

=> file medline cancerlit biosis embase scisearch

COST IN U.S. DOLLARS SINCE FILE TOTAL
ENTRY SESSION
FULL ESTIMATED COST 0.45 0.45

FILE 'MEDLINE' ENTERED AT 11:15:42 ON 17 SEP 1999

FILE 'CANCERLIT' ENTERED AT 11:15:42 ON 17 SEP 1999

FILE 'BIOSIS' ENTERED AT 11:15:42 ON 17 SEP 1999
COPYRIGHT (C) 1999 BIOSIS(R)

FILE 'EMBASE' ENTERED AT 11:15:42 ON 17 SEP 1999
COPYRIGHT (C) 1999 Elsevier Science B.V. All rights reserved.

FILE 'SCISEARCH' ENTERED AT 11:15:42 ON 17 SEP 1999
COPYRIGHT (C) 1999 Institute for Scientific Information (ISI) (R)

=> s (ccr or cell cycle regulatory) and (cdk or cyclin dependent kinase) and (antibod? or monoclon? or ccr binding)

L1 58 (CCR OR CELL CYCLE REGULATORY) AND (CDK OR CYCLIN DEPENDENT
KINASE) AND (ANTIBOD? OR MONOCLON? OR CCR BINDING)

=> dup rem

ENTER L# LIST OR (END):l1

PROCESSING COMPLETED FOR L1
L2 28 DUP REM L1 (30 DUPLICATES REMOVED)

=> d l2 1-28 ibib ab

L2 ANSWER 1 OF 28 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 1999283004 MEDLINE
DOCUMENT NUMBER: 99283004
TITLE: The cyclin kinase inhibitor p21CIP1/WAF1 limits glomerular epithelial cell proliferation in experimental glomerulonephritis.
AUTHOR: Kim Y G; Alpers C E; Brugarolas J; Johnson R J; Couser W G;
Shankland S J
CORPORATE SOURCE: Department of Medicine, University of Washington School of
Medicine, Seattle, Washington, USA.
CONTRACT NUMBER: DK 52121 (NIDDK)
DK34198 (NIDDK)
DK47659 (NIDDK)
SOURCE: KIDNEY INTERNATIONAL, (1999 Jun) 55 (6) 2349-61.
Journal code: KVB. ISSN: 0085-2538.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199909
ENTRY WEEK: 19990902
AB BACKGROUND: During glomerulogenesis, visceral glomerular epithelial cells
(VECs) exit the cell cycle and become terminally differentiated and quiescent. In contrast to other resident glomerular cells, VECs undergo little if any proliferation in response to injury. However, the mechanisms for this remain unclear. Cell proliferation is controlled by cell -cycle regulatory proteins where the cyclin-dependent kinase inhibitor p21Cip1,WAF1 (p21) inhibits cell proliferation and is required for differentiation of many nonrenal cell types. METHODS: To test the hypothesis that p21 is required to maintain a differentiated and quiescent VEC phenotype, experimental glomerulonephritis was induced in p21 knockout (-/-) and p21 wild-type (+/+) mice with antiglomerular antibody. DNA synthesis (proliferating cell nuclear antigen, bromodeoxyuridine staining), VEC proliferation (multilayers of cells in Bowman's space), matrix accumulation (periodic acid-Schiff, silver staining), apoptosis (TUNEL), and renal function (serum urea nitrogen) were studied on days 5 and 14 (N = 6 per time point). VECs were identified by location, morphology, ezrin staining, and electron microscopy. VEC differentiation was measured by staining for Wilms' tumor-1 gene. RESULTS: Kidneys from unmanipulated p21-/- mice were histologically normal and did not have increased DNA synthesis, suggesting that p21 was not required for the induction of VEC terminal differentiation. Proliferating cell nuclear antigen and bromodeoxyuridine staining was increased 4.3- and 3.3-fold, respectively, in p21-/- mice with glomerulonephritis (P < 0.0001 vs. p21+/+ mice). At each time point, VEC proliferation was also increased in nephritic p21-/- mice (P < 0.0001 vs. p21+/+ mice). VEC re-entry into the cell cycle was associated with the loss of Wilms' tumor-1 gene staining. Nephritic p21-/- mice had increased extracellular matrix protein accumulation and apoptosis
and decreased renal function (serum urea nitrogen) compared with p21+/+ mice (P < 0.001). CONCLUSION: These results show that the cyclin kinase inhibitor p21 is not required by VECs to attain a terminally differentiated VEC phenotype. However, the loss of p21, in disease states,
is associated with VEC re-entry into the cell cycle and the development of a dedifferentiated proliferative phenotype.

L2 ANSWER 2 OF 28 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 1999208291 MEDLINE
DOCUMENT NUMBER: 99208291
TITLE: The prognostic significance of proliferation-associated nucleolar protein p120 expression in prostate adenocarcinoma: a comparison with cyclins A and B1, Ki-67, proliferating cell nuclear antigen, and p34cdc2.
AUTHOR: Kallakury B V; Sheehan C E; Rhee S J; Fisher H A; Kaufman R
P Jr; Rifkin M D; Ross J S
CORPORATE SOURCE: Department of Pathology, Albany Medical College, New York
12208, USA.
SOURCE: CANCER, (1999 Apr 1) 85 (7) 1569-76.
Journal code: CLZ. ISSN: 0008-543X.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals; Cancer
Journals
ENTRY MONTH: 199907
ENTRY WEEK: 19990702
AB BACKGROUND: In this study, the authors evaluated the prognostic significance of the expression of nucleolar antigen p120, along with other cell proliferation-associated proteins, in prostate adenocarcinomas (PACs) and compared the results with previously reported data on p34cdc2 cyclin-dependent kinase (p34 cdk).
METHODS: Archival sections from 132 PACs were immunostained with monoclonal antibodies against p120, cyclin A, cyclin B1, Ki-67, and proliferating cell nuclear antigen (PCNA). The DNA content of each tumor was determined by the Feulgen method using image analysis. The
immunohistochemistry (IHC) results were correlated with tumor grade, stage, margin positivity, metastasis, ploidy, and postsurgical disease recurrence. RESULTS: The overall positivity for the various proteins follows: p120, 36%; cyclin A, 35%; cyclin B1, 43%; Ki-67, 46%; and PCNA, 32%. p120 correlated with grade (P = 0.004), stage (P = 0.01), ploidy (P = 0.02), margin positivity (P = 0.03), and metastasis (P = 0.004). Cyclin B1 correlated with ploidy (P = 0.04) and grade (P = 0.05), Ki-67 with grade

(P = 0.02) and margins (P = 0.03), and PCNA with grade (P = 0.01). Significant coexpression among these proteins was noted, as was a significant association between the expression of these markers and that previously reported for p34 cdk. In univariate analysis, p120 (P = 0.01), cyclin A (P = 0.01) and p34 cdk (P = 0.002) correlated with disease recurrence. In multivariate analysis of all these proteins, only p34 cdk independently predicted postsurgical recurrence (P = 0.05). CONCLUSIONS: Nucleolar antigen p120 expression appears to be an additional marker of aggressiveness in PACs. The significant coexpression of the various cell cycle regulatory proteins support their collective role in tumor cell proliferation, with p34 cdk positivity being an independent predictor of postsurgical recurrence.

L2 ANSWER 3 OF 28 BIOSIS COPYRIGHT 1999 BIOSIS
ACCESSION NUMBER: 1999:219154 BIOSIS
DOCUMENT NUMBER: PREV199900219154
TITLE: Regulation of Rb and E2F by signal transduction cascades: Divergent effects of JNK1 and p38 kinases.
AUTHOR(S): Wang, Sheng; Nath, Niharika; Minden, Audrey; Chellappan, Srikumar (1)
CORPORATE SOURCE: (1) Department of Pathology, College of Physicians and Surgeons, Columbia University, 630W 168th Street, New York, NY, 10032 USA
SOURCE: EMBO (European Molecular Biology Organization) Journal, (March 15, 1999) Vol. 18, No. 6, pp. 1559-1570. ISSN: 0261-4189.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The E2F transcription factor plays a major role in cell cycle regulation, differentiation and apoptosis, but it is not clear how it is regulated by non-mitogenic signaling cascades. Here we report that two kinases involved in signal transduction have opposite effects on E2F function: the stress-induced kinase JNK1 inhibits E2F1 activity whereas the related p38 kinase reverses Rb-mediated repression of E2F1. JNK1 phosphorylates E2F1 in vitro, and co-transfection of JNK1 reduces the DNA binding activity of E2F1; treatment of cells with TNFalpha had a similar effect. Fas stimulation of Jurkat cells is known to induce p38 kinase and we find a pronounced increase in Rb phosphorylation within 30 min of Fas stimulation. Phosphorylation of Rb correlated with a dissociation of E2F and increased transcriptional activity. The inactivation of Rb by Fas was blocked by SB203580, a p38-specific inhibitor, as well as a dominant-negative p38 construct; cyclin-dependent kinase (cdk) inhibitors as well as dominant-negative cdks had no effect. These results suggest that Fas-mediated inactivation of Rb is mediated via the p38 kinase, independent of cdks. The Rb/E2F-mediated cell cycle regulatory pathway appears to be a normal target for non-mitogenic signaling cascades and could be involved in mediating the cellular effects of such signals.

L2 ANSWER 4 OF 28 MEDLINE
ACCESSION NUMBER: 1999261885 MEDLINE
DOCUMENT NUMBER: 99261885
TITLE: Dissociation between growth arrest and differentiation in Caco-2 subclone expressing high levels of sucrase.
AUTHOR: Tian J Q; Quaroni A
CORPORATE SOURCE: Section of Physiology, Cornell University, Ithaca, New York 14853, USA.
CONTRACT NUMBER: DK-48331 (NIDDK)
SOURCE: AMERICAN JOURNAL OF PHYSIOLOGY, (1999 May) 276 (5 Pt 1) G1094-104. Journal code: 3U8. ISSN: 0002-9513.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199908
ENTRY WEEK: 19990802
AB Growth arrest and cell differentiation are generally considered temporally and functionally linked phenomena in small intestinal crypt cells and colon tumor cell lines (Caco-2, HT-29). We have derived a Caco-2 subclone (NG13) that deviates from such a paradigm. In striking contrast with the parental cells, proliferative and subconfluent NG13 cells were found to express sucrase-isomaltase (SI) mRNA and to synthesize relatively high levels of SI, dipeptidyl peptidase IV, and aminopeptidase N (APN). In postconfluent cells, little difference was seen in SI mRNA levels between Caco-2 and NG13 cells, but the latter still expressed much higher levels of SI that could be attributed to higher rates of translation. APN expression was also greatly enhanced in NG13 cells. To determine whether high levels of brush-border enzymes correlated with expression of cell-cycle regulatory proteins, we investigated their relative cellular levels in growing and growth-arrested cells. The results showed that the cyclin-dependent kinase inhibitors (p21 and p27) and D-type cyclins (D1 and D3) were all induced in postconfluent cells, but NG13 cells expressed much higher levels of p21. This study demonstrated that cell growth and expression of differentiated traits are not mutually exclusive in intestinal epithelial cells and provided evidence indicating that posttranscriptional events play an important role in regulation of SI expression.

L2 ANSWER 5 OF 28 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1999106669 EMBASE
TITLE: Molecular mechanisms of endothelin-1-induced cell-cycle progression: Involvement of extracellular signal-regulated kinase, protein kinase C, and phosphatidylinositol 3-kinase at distinct points.
AUTHOR: Suzuki E.; Nagata D.; Kakoki M.; Hayakawa H.; Goto A.; Omata M.; Hirata Y.
CORPORATE SOURCE: Dr. E. Suzuki, Second Dept. of Internal Medicine, Faculty of Medicine, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan. suzuki-2im@h.u-tokyo.ac.jp
SOURCE: Circulation Research, (19 Mar 1999) 84/5 (611-619). Refs: 43 ISSN: 0009-7330 CODEN: CIRUAL
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 002 Physiology
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Although it is well established that endothelin-1 (ET-1) has not only vasoconstrictive effects but also mitogenic effects, which seem to be implicated in vascular remodeling, little is known about the molecular mechanisms by which ET-1 induces cell-cycle progression. In this study, we examined the effects of ET-1 on the cell-cycle regulatory machinery, including cyclins, cyclin-dependent kinase (cdk), and cdk inhibitors in NIH3T3 cells. ET-1 increased cyclin D1 protein (5.1 .+-. 1.9-fold increase, 8 hours after stimulation, P < 0.05), cdk4 kinase activity (2.8 .+-. 0.5-fold increase, 12 hours after stimulation, P < 0.01), and cdk2 kinase activity (2.1 .+-. 0.4-fold increase, 16 hours after stimulation, P < 0.05) in a time- and dose-dependent manner. ET-1-induced increase in cyclin D1 protein, and cdk4 kinase activity was not significantly inhibited by an inhibitor of the mitogen-activated protein kinase kinase 1/2, PD98059, nor by the protein kinase C inhibitor calphostin C, whereas ET-1-induced upregulation of cyclin D1 protein and cdk4 kinase activity was significantly inhibited by the phosphatidylinositol 3-kinase inhibitor LY294002. In contrast, ET-1-induced activation of cdk2 kinase was significantly inhibited by PD98059, calphostin C, and LY294002. ET-1 increased 3H-thymidine uptake in a time-dependent fashion (0 hours, 4216 .+-. 264 cpm per well; 8 hours, 5025 .+-. 197 cpm per well; 16 hours, 9239 .+-. 79 cpm per well, P < 0.001 versus 0 hours). ET-1- induced increase in 3H-thymidine uptake was significantly inhibited by PD98059, calphostin C, and LY294002. These results suggest that ET-1-induced cell-cycle progression is, at least in part, mediated by the extracellular signal-regulated kinase, protein kinase C, and phosphatidylinositol 3-kinase and that those pathways may be involved in the progression of the cell cycle at distinct points.

L2 ANSWER 6 OF 28 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1999263216 EMBASE
TITLE: Complement (C5b-9) induces glomerular epithelial cell DNA synthesis but not proliferation in vitro.
AUTHOR: Shankland S.J.; Pippin J.W.; Couser W.G.
CORPORATE SOURCE: Dr. S.J. Shankland, Division of Nephrology, University of Washington, P.O. Box 356521, Seattle, WA 98195, United States. stuartjs@u.washington.edu
SOURCE: Kidney International, (1999) 56/2 (538-548). Refs: 53 ISSN: 0085-2538 CODEN: KDYIA5
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
026 Immunology, Serology and Transplantation
028 Urology and Nephrology
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Background. The C5b-9 membrane attack complex of complement is the principal mediator of injury induced experimentally by antibodies directed at glomerular cell membranes. In experimental membranous nephropathy, C5b-9 induced injury to the glomerular visceral epithelial cell (VEC) is associated with DNA synthesis, but not cytokinesis. In the current study we determined if C5b-9 increases DNA synthesis in VEC in vitro, and defined the mechanisms involved. Methods. Rat VEC in vitro were divided into three groups: (1) sensitized with anti-VEC antibody and exposed to sublytic concentrations of C+/PVG serum (normal complement components); (2) anti-VEC antibody and control C-/PVG serum (C6 deficient); (3) no anti-VEC antibody. DNA synthesis (BrdU staining), mitosis (mitotic figures) and cytokinesis (cell counts) were measured at 24 and 48 hours. To examine the expression of specific S-phase

and M-phase cell cycle regulatory proteins and their inhibitors, immunostaining and Western blot analysis was performed for cyclin A, CDK2, p21 and p27, cyclin B and cdc2. Results. In the absence of growth factors, sublytic C5b-9 attack did not increase proliferation. In contrast, sublytic C5b-9 attack (group 1) augmented growth factor induced DNA synthesis by 50% compared to controls (groups 2 and 3; P < 0.001), and was accompanied by increased levels of cyclin A and CDK2, and a decrease in the cyclin kinase inhibitor p27 (but not p21). Sublytic C5b-9 attack reduced the expression of the M phase cell cycle proteins, cyclin B and cdc2, accompanied by reduced mitosis (mitotic figures) and cytokinesis (cell number). Conclusions. Our results show that the C5b-9 augmented growth factor entry into the S phase in VEC is regulated by changes in specific cell cycle regulatory proteins. However, antibody and complement decreased the M phase cell cycle proteins, and prevented VEC mitosis and cytokinesis, suggesting a delay or arrest at the G2/M phase.

L2 ANSWER 7 OF 28 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.DUPLICATE 3
ACCESSION NUMBER: 1999301312 EMBASE
TITLE: Immunochemical analysis of the D-type cyclin-dependent kinases Cdk4 and Cdk6, using a series of monoclonal antibodies.
AUTHOR: Lukas C.; Jensen S.S.; Bartkova J.; Lukas J.; Bartek J.
CORPORATE SOURCE: J. Bartek, Dept. Cell Cycle and Cancer, Institute of Cancer Biology, Danish Cancer Society, Strandboulevarden 49, DK-2100 Copenhagen, Denmark
SOURCE: Hybridoma, (1999) 18/3 (225-234).
Refs: 25
ISSN: 0272-457X CODEN: HYBRDY
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 026 Immunology, Serology and Transplantation
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Cellular signal transduction cascades triggered by mitogenic or antiproliferative cues eventually converge on a biochemical mechanism centered around the retinoblastoma tumor suppressor (pRb), the so-called RB pathway that governs G1-phase progression and guards the commitment to enter S phase. pRb, together with its immediate upstream regulators, the D-type cyclins, their partner cyclin-dependent kinases Cdk4 and Cdk6, and the Cdk inhibitors, form a functional unit that is involved in major decisions about cellular fate, and whose components, including the proto-oncogenic cyclin D- dependent kinases, are commonly deregulated in many types of cancer. We report here the production and characterization of a series of 12 monoclonal antibodies (MAbs) that specifically recognize either Cdk4 or Cdk6. These antibodies are proving to be invaluable molecular probes for defining abundance, subcellular localization, binding partners, and ultimately the function(s) of these cell cycle-regulatory kinases. Localization of the target epitopes was mapped by peptide enzyme-linked immunoadsorbent assay (ELISA), and two antibodies recognizing sequences adjacent to N-terminus of Cdk4 can discriminate between the wild-type protein and the oncogenic, melanoma-associated R24C mutant of this kinase. Individual antibodies of our panel recognize distinct pools of Cdk4/6, a feature reflected by their differential applicability in immunoblotting, immunoprecipitation, kinase assays, and immunostaining including immunohistochemistry on archival paraffin-embedded tissue sections. Collectively, the antibodies described in this study provide the means for immunochemical analyses of the cyclin D- dependent kinases in human and animal cells, and represent useful molecular tools that should help better understand the biological roles of Cdk4 and Cdk6 in normal cell-cycle control, and their oncogenic activity in tumor cells.

L2 ANSWER 8 OF 28 MEDLINE
ACCESSION NUMBER: 1999254822 MEDLINE
DOCUMENT NUMBER: 99254822
TITLE: Functional analysis of the p57KIP2 gene mutation in Beckwith-Wiedemann syndrome.
AUTHOR: Bhuiyan Z A; Yatsuki H; Sasaguri T; Joh K; Soejima H; Zhu X; Hatada I; Morisaki H; Morisaki T; Mukai T
CORPORATE SOURCE: Department of Bioscience, National Cardiovascular Center Research Institute, Suita, Osaka, Japan.
SOURCE: HUMAN GENETICS, (1999 Mar) 104 (3) 205-10.
Journal code: GED. ISSN: 0340-6717.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199907
ENTRY WEEK: 19990705
AB p57KIP2 is a potent tight-binding inhibitor of several G1 cyclin/cyclin-dependent kinase (Cdk) complexes, and is a negative regulator of cell proliferation. The gene encoding p57KIP2 is located at 11p15.5, a region implicated in both sporadic cancers and Beckwith-Wiedemann syndrome (BWS). Previously we demonstrated that p57KIP2 is imprinted and only the maternal allele is expressed in both mice and humans. We also showed mutations found in p57KIP2 in patients with BWS that were transmitted from the patients' carrier mothers, indicating that the expressed maternal allele was mutant and that the repressed paternal allele was normal. In the study reported here, we performed functional analysis of the two mutated p57KIP2 genes. We showed that the nonsense mutation found in the Cdk inhibitory domain in a BWS patient rendered the protein inactive with consequent complete loss of its role as a cell cycle inhibitor and of its nuclear localization. We also showed that the mutation in the QT domain, although completely retaining its cell cycle regulatory activity, lacked nuclear localization and was thus prevented from performing its role as an active cell cycle inhibitor. Consequently, no active p57KIP2 would have existed, which might have caused the disorders in BWS patients.

L2 ANSWER 9 OF 28 SCISEARCH COPYRIGHT 1999 ISI (R)
ACCESSION NUMBER: 1999:504327 SCISEARCH
THE GENUINE ARTICLE: 209ZZ
TITLE: Effects of lovastatin on expression of cell cycle regulatory proteins in vascular smooth muscle cells
AUTHOR: Oda H; Kasiske B L; ODonnell M (Reprint); Keane W F
CORPORATE SOURCE: MINNEAPOLIS MED RES FDN INC, 914 S 8TH ST, MINNEAPOLIS, MN
55404 (Reprint); HENNEPIN CTY MED CTR, DEPT MED, DIV NEPHROL, MINNEAPOLIS, MN 55415
COUNTRY OF AUTHOR: USA
SOURCE: KIDNEY INTERNATIONAL, (JUL 1999) Vol. 56, Supp. [71], pp. S202-S205.
Publisher: BLACKWELL SCIENCE INC, 350 MAIN ST, MALDEN, MA
02148.
ISSN: 0085-2538.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE; CLIN
LANGUAGE: English
REFERENCE COUNT: 11
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB Background. The sequential appearance of cyclins D and E is thought to initiate subsequent DNA synthesis in proliferating cells. Previous studies have reported that DNA synthesis in cultured rat vascular smooth muscle cells (VSMCs) was suppressed by the HMG-CoA reductase inhibitor lovastatin. The effects of lovastatin on cell cycle regulatory proteins in proliferating VSMCs, however, are largely unknown. Thus, we investigated the sequential expression of cyclin D1, cyclin E, cyclin-dependent kinase (CDK) 4, CDK2, and p27Kip1 in cultured rat VSMCs stimulated by platelet-derived growth factor (PDGF)-BB in the presence or absence of lovastatin.
Methods. Quiescent VSMCs, with and without lovastatin (20 mu M) pretreatment for nine hours, were stimulated by PDGF-BB (25 ng/ml). The incorporation of tritiated thymidine was done to assess DNA synthesis. VSMC lysates were obtained every 6 hours for up to 36 hours after stimulation and were subjected to sodium dodecyl sulfate-polyacrylamide gel electrophoresis and Western blot analysis using relevant polyclonal antibodies. Autoradiograms were analyzed using a densitometer.
Results. The peak expression of cyclins D1 and E occurred at 18 and 30 hours of PDGF stimulation, respectively. Concomitant expression of CDK4 and CDK2 was also observed. The expression of p27Kip1. by contrast, was reduced in association with DNA synthesis. Lovastatin suppressed DNA synthesis and reduced the expression of cyclin D1 and cyclin E, whereas p27Kip1 expression was strongly induced by lovastatin pretreatment. CDK4 and CDK2 expression was unaffected by lovastatin treatment.
Conclusions. PDGF-BB induces cyclins D1 and E prior to the onset of DNA synthesis in VSMCs. Lovastatin may suppress DNA synthesis in VSMCs by inducing p27Kip1 and reducing expression of cyclins D1 and E.

L2 ANSWER 10 OF 28 BIOSIS COPYRIGHT 1999 BIOSIS DUPLICATE 4
ACCESSION NUMBER: 1999:357709 BIOSIS
DOCUMENT NUMBER: PREV199900357709
TITLE: Effects of lovastatin on expression of cell cycle regulatory proteins in vascular smooth muscle cells.
AUTHOR(S): Oda, Hiroaki; Kasiske, Bertram L.; O'Donnell, Michael P. (1); Keane, William F.
CORPORATE SOURCE: (1) Minneapolis Medical Research Foundation, 914 South Eighth Street, Minneapolis, MN, 55404 USA
SOURCE: Kidney International Supplement, (July, 1999) Vol. 0, No. 71, pp. S.202-S.205.
ISSN: 0098-6577.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Background. The sequential appearance of cyclins D and E is thought to initiate subsequent DNA synthesis in proliferating cells. Previous studies have reported that DNA synthesis in cultured rat vascular smooth muscle cells (VSMCs) was suppressed by the HMG-CoA reductase inhibitor

lovastatin. The effects of lovastatin on cell cycle regulatory proteins in proliferating VSMCs, however, are largely unknown. Thus, we investigated the sequential expression of cyclin D1, cyclin E, cyclin-dependent kinase (CDK) 4, CDK2, and p27Kip1 in cultured rat VSMCs stimulated by platelet-derived growth factor (PDGF)-BB in the presence or absence of lovastatin. Methods. Quiescent VSMCs, with and without lovastatin (20 muM) pretreatment for nine hours, were stimulated by PDGF-BB (25 ng/ml). The incorporation of tritiated thymidine was done to assess DNA synthesis. VSMC lysates were obtained every 6 hours for up to 36 hours after stimulation and were subjected to sodium dodecyl sulfate-polyacrylamide gelelectrophoresis and Western blot analysis using relevant polyclonal antibodies. Autocardiograms were analyzed using a densitometer. Results. The peak expression of cyclins D1 and E occurred at 18 and 30 hours of PDGF stimulation, respectively. Concomitant expression of CDK4 and CDK2 was also observed. The expression of p27Kip1, by contrast, was reduced in association with DNA synthesis. Lovastatin suppressed DNA synthesis and reduced the expression of cyclin D1 and cyclin E, whereas p27Kip1 expression was strongly induced by lovastatin pretreatment. CDK4 and CDK2 expression was unaffected by lovastatin treatment. Conclusions. PDGF-BB induces cyclins D1 and E prior to the onset of DNA synthesis in VSMCs. Lovastatin may suppress DNA synthesis in VSMCs by inducing p27Kip1 and reducing expression of cyclins D1 and E.

L2 ANSWER 11 OF 28 CANCERLIT
ACCESSION NUMBER: 1999261885 CANCERLIT
DOCUMENT NUMBER: 99261885
TITLE: Dissociation between growth arrest and differentiation in Caco-2 subclone expressing high levels of sucrase.
AUTHOR: Tian J Q; Quaroni A
CORPORATE SOURCE: Section of Physiology, Cornell University, Ithaca, New York 14853, USA.
CONTRACT NUMBER: DK-48331 (NIDDK)
SOURCE: AMERICAN JOURNAL OF PHYSIOLOGY, (1999). 276 (5 Pt. 1):G1094-104. Journal code: 3U8. ISSN: 0002-9513.
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
FILE SEGMENT: MEDL; L; Priority Journals
LANGUAGE: English
OTHER SOURCE: MEDLINE 99261885
ENTRY MONTH: 199907
AB Growth arrest and cell differentiation are generally considered temporally and functionally linked phenomena in small intestinal crypt cells and colon tumor cell lines (Caco-2, HT-29). We have derived a Caco-2 subclone (NGI3) that deviates from such a paradigm. In striking contrast with the parental cells, proliferative and subconfluent NGI3 cells were found to express sucrase-isomaltase (SI) mRNA and to synthesize relatively high levels of SI, dipeptidyl peptidase IV, and aminopeptidase N (APN). In postconfluent cells, little difference was seen in SI mRNA levels between Caco-2 and NGI3 cells, but the latter still expressed much higher levels of SI that could be attributed to higher rates of translation. APN expression was also greatly enhanced in NGI3 cells. To determine whether high levels of brush-border enzymes correlated with expression of cell-cycle regulatory proteins, we investigated their relative cellular levels in growing and growth-arrested cells. The results showed that the cyclin-dependent kinase inhibitors (p21 and p27) and D-type cyclins (D1 and D3) were all induced in postconfluent cells, but NGI3 cells expressed much higher levels of p21. This study demonstrated that cell growth and expression of differentiated traits are not mutually exclusive in intestinal epithelial cells and provided evidence indicating that posttranscriptional events play an important role in regulation of SI expression.

L2 ANSWER 12 OF 28 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1999229512 EMBASE
TITLE: Effect of simvastatin on proliferative nephritis and cell-cycle protein expression.
AUTHOR: Yoshimura A.; Nemoto T.; Sugenoya Y.; Inui K.; Watanabe S.; Inoue Y.; Sharif S.; Yokota N.; Uda S.; Marita H.; Ideura T.
CORPORATE SOURCE: Dr. A. Yoshimura, Department of Medicine, Division of Nephrology, Showa University, 1-30 Fujigaoka, Aoba-ku, Yokohama 227-8501, Japan
SOURCE: Kidney International, Supplement, (1999) 56/71 (S84-S87). Refs: 10 ISSN: 0098-6577 CODEN: KISUDF
COUNTRY: United States
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 028 Urology and Nephrology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Background. Mesangial cell proliferation is important in subsequent mesangial matrix expansion in glomerular injury. Therefore, the regulation of mesangial cell proliferation may be critical in the treatment of glomerulonephritis. Inhibition of 3-hydro-3-methylglutaryl coenzyme A (HMG- CoA) reductase inhibits the production of mevalonate and has been shown to suppress proliferation in many cell types, including mesangial cells in vitro. It is expected that HMG-CoA reductase inhibitor may suppress mesangial cell proliferation and subsequent progression of glomerulonephritis. Recently, the tight relationship between cell -cycle regulatory protein expression and mesangial cell proliferation in experimental glomerulonephritis was demonstrated. The aim of the present study is to examine the effect of simvastatin, one of the HMG-CoA reductase inhibitors, on the glomerular cell proliferation and on the expression of CDK2 or p27Kip1 in mesangial cells in experimental glomerulonephritis in vivo. Methods. The effect of simvastatin on a rat mesangial proliferative glomerulonephritis induced by antithymocyte antibody (anti-Thy 1.1 GN) was studied. Administration of simvastatin or vehicle (for control GN) were started from two days before disease induction, and was continued to the day of nephrectomy. Nephrectomy was done at days 0, 2, 4, 7, 12 and 20 after disease induction. Immunohistochemistry for proliferating cells, macrophages, .alpha.- smooth muscle actin, type IV collagen and PDGF-B chain was performed, respectively, in addition to conventional periodic-acid Schiff staining. Double immunostaining for CDK2/OX-7 or p27Kip1/OX-7 was also done, respectively. Results. There was no difference in the degree of the initial injuries between simvastatin-treated and control GN rats. The most pronounced feature of simvastatin-treated GN was the suppression of the early glomerular cell proliferation (about 70% of proliferation was suppressed at day 4). At day 4, .alpha.-smooth muscle actin expression was also decreased in simvastatin- treated GN rats. Inhibition of macrophage recruitment into glomeruli by simvastatin was also a prominent feature (about 30% decrease in the number of glomerular macrophages at day 2). Simvastatin significantly suppressed subsequent mesangial matrix expansion and type IV collagen accumulation in glomeruli. Although it might simply reflect the reduction in mesangial cells, glomerular PDGF-B chain expression was reduced. There was no significant difference in plasma lipids levels at day 2 and day 4. In vehicle-treated GN rats, the number of CDK2+/OX-7+ cells (CDK2-expressed mesangial cells) in glomeruli increased significantly from day 4 to day 7. Although simvastatin suppressed mesangial cell proliferation, the increase in the number of glomerular CDK2+/OX-7+ cells was also attenuated by simvastatin treatment. There was no difference in the number of p27Kip1+/OX-7+cells (p27Kip1- expressed mesangial cells) in the glomerulus between vehicle-treated and simvastatin-treated GN rats. Conclusion. Simvastatin suppressed mesangial cell proliferation and subsequent matrix expansion, and macrophage infiltration into glomeruli in anti-Thy 1.1 GN rats. The antiproliferative effect of simvastatin in this model was also associated with the reduction of CDK2 expression in mesangial cells.

L2 ANSWER 13 OF 28 MEDLINE DUPLICATE 5
ACCESSION NUMBER: 1998240990 MEDLINE
DOCUMENT NUMBER: 98240990
TITLE: A flavonoid antioxidant, silymarin, inhibits activation of erbB1 signaling and induces cyclin-dependent kinase inhibitors, G1 arrest, and anticarcinogenic effects in human prostate carcinoma DU145 cells.
AUTHOR: Zi X; Grasso A W; Kung H J; Agarwal R
CORPORATE SOURCE: Department of Dermatology, Case Western Reserve University, Cleveland, Ohio 44106, USA.
CONTRACT NUMBER: CA 64514 (NCI)
P30-CA 43703 (NCI)
SOURCE: CANCER RESEARCH, (1998 May 1) 58 (9) 1920-9. Journal code: CNF. ISSN: 0008-5472.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199808
ENTRY WEEK: 19980801
AB Prostate cancer (PCA) is the most common nonskin malignancy and the second leading cause of cancer deaths in United States males. One practical and translational approach to control PCA is to define a mechanism-based anticarcinogenic agent(s). Recently, we showed that silymarin, a flavonoid antioxidant isolated from milk thistle, possesses exceptionally high to complete protective effects against experimentally induced tumorigenesis. Because the epidermal growth factor receptor (erbB1) and other members of the erbB family have been shown to play important roles in human PCA, efforts should be directed to identify inhibitors of this pathway for PCA intervention. In this study, we assessed whether silymarin inhibits erbB1 activation and associated downstream events and modulates cell cycle regulatory proteins and progression, leading to growth inhibition of human prostate carcinoma DU145 cells. Treatment of serum-starved cells with silymarin resulted in a significant inhibition of transforming growth factor alpha-mediated activation of erbB1 but no change in its protein levels. Silymarin treatment of cells also resulted in a significant decrease in tyrosine phosphorylation of an immediate downstream target of erbB1, the adapter protein SHC, together with a

decrease in its binding to erbB1. In the studies analyzing cell cycle regulatory molecules, silymarin treatment of cells also resulted in a significant induction of cyclin-dependent kinase inhibitors (CDKIs) Cip1/p21 and Kip1/p27, concomitant with a significant decrease in CDK4 expression, but no change in the levels of CDK2 and CDK6 and their associated cyclins E and D1, respectively. Cells treated with silymarin also showed an increased binding of CDKIs with CDKs, together with a marked decrease in the kinase activity of CDKs and associated cyclins. In additional studies, treatment of cells grown in 10% serum with anti-epidermal growth factor receptor monoclonal antibody clone 225 or different doses of silymarin also resulted in significant inhibition of constitutive tyrosine phosphorylation of both erbB1 and SHC but no change in their protein levels. Furthermore, whereas silymarin treatment resulted in a significant increase in the protein levels of both Cip1/p21 and Kip1/p27, monoclonal antibody 225 showed an increase only in Kip1/p27. These findings suggest that silymarin also inhibits constitutive activation of erbB1 and that the observed effect of silymarin on an increase in CDKI protein levels is mediated via inhibition of erbB1 activation only in the case of Kip1/p27; however, additional pathways independent of inhibition of erbB1 activation are possibly responsible for the silymarin-caused increase in Cip1/p21 in DU145 cells. In other studies, silymarin treatment also induced a G1 arrest in the cell cycle progression of DU145 cells and resulted in a highly significant to complete inhibition of both anchorage-dependent and anchorage-independent growth of DU145 cells in a dose- and time-dependent manner. Taken together, these results suggest that silymarin may exert a strong anticarcinogenic effect against PCA and that this effect is likely to involve impairment of erbB1-SHC-mediated signaling pathway, induction of CDKIs, and a resultant G1 arrest.

L2 ANSWER 14 OF 28 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.DUPLICATE 6
ACCESSION NUMBER: 1998152192 EMBASE
TITLE: Immunohistochemical detection of sex steroid receptors, cyclins, and cyclin-dependent kinases in the normal and neoplastic squamous epithelia of the uterine cervix.
AUTHOR: Kanai M.; Shiozawa T.; Xin L.; Nikaido T.; Fujii S.
CORPORATE SOURCE: Dr. S. Fujii, Department of Obstetrics/Gynecology, Shinshu University Sch. of Medicine, 3-1-1 Asahi, Matsumoto 390, Japan
SOURCE: Cancer, (1 May 1998) 82/9 (1709-1719).
Refs: 50
ISSN: 0008-543X CODEN: CANCAR
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
010 Obstetrics and Gynecology
016 Cancer
LANGUAGE: English
SUMMARY LANGUAGE: English
AB BACKGROUND: Malignant transformation of sex steroid-dependent tissues has been reported to associated with abnormal expression of sex steroid receptors. In addition, abnormalities of cell-cycle molecules have been demonstrated in various malignancies. However, expression of steroid receptors and cell cycle-related molecules in the process of malignant transformation of the ectocervical squamous epithelium, which also is sex steroid-dependent tissue, has not been elucidated fully. METHODS: Immunohistochemical staining was performed on formalin fixed, paraffin embedded tissue section of normal squamous epithelia (30 cases), cervical intraepithelial neoplasia (CIN) (21 cases), and invasive squamous carcinoma (SCC) (33 cases), using antibodies against estrogen receptors (ER), progesterone receptors (PR), cyclins (E, A, and B1), cyclin-dependent kinases (cdk2 and cdc2), and p53 protein. In addition, growth activity of SCC was evaluated by Ki-67 labeling. RESULTS: In the normal epithelia, diffuse proportionate to regional expression of ER/PR and sporadic expression of cyclins/cdks were observed mainly in the parabasal cells irrespective of the menstrual cycle. In the neoplastic lesion, the expression of ER markedly decrease; however, the expression of PR increased. The expression of cyclins, cdks, and p52 was increased in a considerable number of these neoplastic cases. In addition, cyclin A positive SCC had elevated Ki-67 labeling, whereas cyclin E positive SCC cases had lower Ki-67 labeling. CONCLUSION: These findings suggest that malignant transformation of ectocervical epithelia is associated with loss of normal growth control by steroid hormones as well as with the acquisition of abnormal cell cycle regulatory mechanisms.

L2 ANSWER 15 OF 28 SCISEARCH COPYRIGHT 1999 ISI (R)
ACCESSION NUMBER: 1998:564339 SCISEARCH
THE GENUINE ARTICLE: 101DJ
TITLE: Expression of the cell-cycle-related proteins E2F-1, p53, mdm-2, p21(waf-1), and Ki-67 in multiple myeloma: Correlation with cyclin-D1 immunoreactivity
AUTHOR: Lai R; Medeiros L J; Wilson C S; Sun N C J; Koo C; McCourty A; Brynes R K (Reprint)
CORPORATE SOURCE: UNIV SO CALIF, SCH MED, DEPT PATHOL, 2011 ZONAL AVE, HMR204, LOS ANGELES, CA 90033 (Reprint); CITY HOPE NATL MED CTR, DIV PATHOL, DUARTE, CA 91010; UNIV ARKANSAS MED SCI, DEPT PATHOL, LITTLE ROCK, AR 72205; HARBOR UNIV CALIF LOS ANGELES, DEPT PATHOL, TORRANCE, CA; KAISER FDN HOSP, DEPT PATHOL, LOS ANGELES, CA
COUNTRY OF AUTHOR: USA
SOURCE: MODERN PATHOLOGY, (JUL 1998) Vol. 11, No. 7, pp. 642-647.
Publisher: WILLIAMS & WILKINS, 351 WEST CAMDEN ST, BALTIMORE, MD 21201-2436.
ISSN: 0893-3952.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE; CLIN
LANGUAGE: English
REFERENCE COUNT: 30
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB Approximately 30% of multiple myelomas (MMs) express cyclin D1 when assessed using immunohistochemical techniques. Cyclin D1 expression correlates with greater tumor burden in MM, because cyclin D1-positive cases are more frequently associated with extensive bone marrow involvement, i.e., high pathologic stage, than are cyclin D1-negative cases. The mechanisms that explain this association are unknown. To explore other differences between cyclin D1-positive and cyclin D1-negative MMs, we assessed 59 MMs immunohistochemically for several G(1) cell-cycle regulatory proteins, including cyclin D1, E2F-1, p53, mdm-2 and p21(waf-1),using routinely fixed and processed, paraffin-embedded bone marrow specimens. Twenty MMs (34%) were cyclin D1 positive, and 39 (66%) were cyclin D1 negative. Eighteen (90%) of 20 cyclin D1-positive MMs were Stage III, in contrast to 19 (49%) of 39 cyclin D1-negative MMs (P = .003). Cyclin D1-positive MMs were more likely to express E2F-1 (16/20 vs. 4/39, P < .001), p53 (11/20 vs. 10/39, P = .041), and p21(waf-1) (12/20 vs. 7/39, P = .003). There was no significant difference in mdm-2 expression between these groups. We also assessed proliferation rate using an antibody specific for the Ki-67 antigen. A relatively high percentage (> 20%) of Ki-67-positive cells was found in cyclin D1-positive MMs compared with cyclin D1-negative MMs (13/20 vs. 3/39, P < 0.001). These results suggest that cyclin D1-positive MMs are more likely to possess additional derangements involving other G(1) cell-cycle regulatory proteins. We speculate that these abnormalities might result in increased proliferation, thereby explaining the correlation between cyclin D1 expression and greater tumor burden.

L2 ANSWER 16 OF 28 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1998263518 EMBASE
TITLE: Cell dynamics in the embryonic and postnatal vomeronasal epithelium of snakes.
AUTHOR: Holtzman D.A.
CORPORATE SOURCE: D.A. Holtzman, Dept. of Brain and Cognitive Sci., University of Rochester, 105 Meliora Hall, Rochester, NY 14627, United States. holtzman@bcs.rochester.edu
SOURCE: Microscopy Research and Technique, (1998) 41/6 (471-482).
Refs: 64
ISSN: 1059-910X CODEN: MRTEEO
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 008 Neurology and Neurosurgery
021 Developmental Biology and Teratology
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
AB This review will discuss changes observed in the cell dynamics of the vomeronasal epithelium (VNE) of snakes during embryonic and postnatal growth. Recent work suggests that neuronal differentiation occurs early in VNE development. We have used an antibody to an evolutionarily conserved peptide sequence (the PSTAIRE region) in a family of cell cycle regulatory proteins, the cyclin-dependent kinases, to identify neuronal precursors in the embryonic and postnatal VNE. During prenatal development, the location of neuronal precursors changes in the VNE. Significant postnatal changes occur in cell proliferation in the VNE (as determined by 3H-thymidine autoradiography) and possibly in the larger complement of VNE receptor cell precursors (as determined by anti-PSTAIRE staining). A model is proposed for changes in cell proliferation and death during embryonic development and postnatal maintenance and senescence in VNE of snakes, which may be applicable to the VNE and olfactory epithelium of other vertebrates.

L2 ANSWER 17 OF 28 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.DUPLICATE 7
ACCESSION NUMBER: 1998217331 EMBASE
TITLE: Immunohistochemical analysis of cell cycle regulatory gene products in normal trophoblast and placental site trophoblastic tumor.
AUTHOR: Ichikawa N.; Zhai Y.-L.; Shiozawa T.; Toki T.; Noguchi H.;

Nikaido T.; Fujii S.
CORPORATE SOURCE: Dr. S. Fujii, Department of Obstetrics/Gynecology, Shinshu
Univ. School of Medicine, 3-1-1 Asahi, Matsumoto 390, Japan
SOURCE: International Journal of Gynecological Pathology, (1998) 17/3 (235-240).
Refs: 34
ISSN: 0277-1691 CODEN: IJGPDR
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
010 Obstetrics and Gynecology
016 Cancer
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Intermediate trophoblast (IT) rarely gives rise to a placental site trophoblastic tumor (PSTT). To examine the different growth mechanisms present in normal and neoplastic IT, the expression of **cell cycle regulatory** molecules was compared at normal implantation sites and in PSTTs. Normal implantation sites in early gestation (19 patients) and PSTTs (6 patients) were *immunohistochemically* studied using **antibodies** against cytokeratin, human chorionic gonadotropin, and human placental lactogen to identify IT, and **antibodies** against Ki-67, cyclins (A, B, D1, and E), cyclin-dependent kinases (cdks), and p53 to investigate the proliferative activity of the trophoblast. Marked proliferative activity was observed in the trophoblast of the cell columns. Normal IT exhibited a very low labeling index for Ki-67, with negative expression for cdks and cyclins, except for cyclins B and E. The tumor cells of PSTT exhibited a high labeling index for Ki-67 with positive expression for all the cyclins and cdks examined. Expression of p53 was identified in tumor cells of PSTTs and the distribution of p53-positive cells correlated topographically with that of the cyclin A-positive cells. The transformed IT of PSTT has high proliferative activity with an abnormal expression of **cell cycle regulatory** molecules, which is not observed in normal IT.

L2 ANSWER 18 OF 28 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1998014610 EMBASE
TITLE: Identification of DNA replication and cell cycle proteins that interact with PCNA.
AUTHOR: Loor G.; Zhang S.-J.; Zhang P.; Toomey N.L.; Lee M.Y.W.
CORPORATE SOURCE: M.Y.W. Lee, New York Medical College, Dept Biochemistry
Molecular Biology, Valhalla, NY 10595, United States.
mlee@mednet.med.miani.edu
SOURCE: Nucleic Acids Research, (15 Dec 1997) 25/24 (5041-5046).
Refs: 54
ISSN: 0305-1048 CODEN: NARHAD
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The identity of DNA replication proteins and **cell cycle regulatory** proteins which can be found in complexes involving PCNA were investigated by the use of PCNA immobilized on Sepharose 4B. A column containing bovine serum albumin (BSA) bound to Sepharose was used as a control. Fetal calf thymus extracts were chromatographed on PCNA-Sepharose and BSA-Sepharose. The columns were washed and then eluted with 0.5 M KCl. The salt eluates were examined for the presence of both DNA replication proteins (pol .alpha., .delta., .epsilon., PCNA, RFC, RFA, DNA ligase I, NDH II, Topo I and Topo II) and cell cycle proteins (Cyclins A, B1, D1, D2, D3, E, CDK2, CDK4, CDK5 and p21) by western blotting with specific **antibodies**. The DNA replication proteins which bound to PCNA-Sepharose included DNA polymerase .delta. and .epsilon., PCNA, the 37 and 40 kDa subunits of RFC, the 70 kDa subunit of RPA, NDH II and topoisomerase I. No evidence for the binding of DNA polymerase .alpha., DNA ligase I or topoisomerase II was obtained. Of the cell cycle proteins investigated, CDK2, CDK4 and CDK5 were bound. This study presents strong evidence that PCNA is a component of protein complexes containing DNA replication, repair and **cell cycle regulatory** proteins.

L2 ANSWER 19 OF 28 MEDLINE DUPLICATE 8
ACCESSION NUMBER: 97188363 MEDLINE
DOCUMENT NUMBER: 97188363
TITLE: Overexpression of c-fos inhibits down-regulation of a **cyclin-dependent kinase**-2 inhibitor p27Kip1 in splenic B cells activated by surface Ig cross-linking.
AUTHOR: Kobayashi K; Phuchareon J; Inada K; Tomita Y; Koizumi T; Hatano M; Miyatake S; Tokuhisa T
CORPORATE SOURCE: Division of Developmental Genetics, Chiba University School of Medicine, Japan.
SOURCE: JOURNAL OF IMMUNOLOGY, (1997 Mar 1) 158 (5) 2050-6.
Journal code: IFB. ISSN: 0022-1767.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals; Cancer Journals
ENTRY MONTH: 199705
ENTRY WEEK: 19970503
AB Splenic B cells activated by surface Ig (sIg) cross-linking transiently express the c-fos gene within 0.5 h and then enter into S phase of the cell cycle within 48 h. To investigate a role of c-fos in cell cycle progression, we used splenic B cells from IFN-alphabeta-inducible c-fos transgenic mice (Mx-c-fos). In the absence of IFN, the cell cycle progression of Mx-c-fos B cells stimulated with anti-IgM Ab was similar to that in control B cells. The cell cycle was arrested in G1 phase when we added IFN to the culture within 12 h after anti-IgM Ab stimulation, suggesting that overexpression of c-fos until mid-G1 phase perturbs activation of the **cell cycle regulatory** machinery. In control B cells, cyclin E and cdk2 were induced within 24 to 48 h after stimulation, and this induction was accompanied by down-regulation of a cdk2 inhibitor p27Kip1. As a consequence of these activation processes, cdk2 kinase activity was induced in B cells in the late G1 phase. However, kinase activity was not detected in Mx-c-fos B cells, presumably because the down-regulation of p27 was perturbed. These data suggest that c-Fos can negatively control **cell cycle regulatory** machinery in sIg-stimulated B cells.

L2 ANSWER 20 OF 28 MEDLINE DUPLICATE 9
ACCESSION NUMBER: 97409635 MEDLINE
DOCUMENT NUMBER: 97409635
TITLE: Cyclin kinase inhibitors are increased during experimental membranous nephropathy: potential role in limiting glomerular epithelial cell proliferation in vivo.
AUTHOR: Shankland S J; Floege J; Thomas S E; Nangaku M; Hugo C; Pippin J; Henne K; Hockenberry D M; Johnson R J; Couser W G
CORPORATE SOURCE: Department of Nephrology, University of Washington, Seattle, USA.. stuartjs@u.washington.edu .
CONTRACT NUMBER: DK34198 (NIDDK)
DK43422 (NIDDK)
DK51096 (NIDDK)
SOURCE: KIDNEY INTERNATIONAL, (1997 Aug) 52 (2) 404-13.
Journal code: KVB. ISSN: 0085-2538.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199801
AB The inadequate proliferative response of the visceral glomerular epithelial cell (GEC) following injury in vivo may contribute to the development of progressive glomerulosclerosis in many forms of glomerular disease. Cell proliferation is ultimately controlled by **cell-cycle regulatory** proteins, including cyclins that bind to cyclin dependent kinases (**CDK**), and the active complex formed is necessary for progression through the cell-cycle. By inhibiting cyclin-**CDK** complexes, cyclin kinase inhibitors arrest the cell-cycle and prevent proliferation. To determine the mechanisms that may be responsible for the lack of GEC proliferation in vivo, we examined GEC expression of specific cell-cycle proteins in normal rats and in the passive Heymann nephritis (PHN) model of membranous nephropathy, where the GEC are the target of complement-mediated injury. Following **antibody**-deposition and complement activation there was a marked up-regulation in the cyclin kinase inhibitors p21 and p27 in rats with PHN. By associating with cyclin A-CDK2 complexes, p21 and p27 limited the kinase activity of CDK2. Giving bFGF to rats with PHN was associated with an increase in GEC mitosis and ploidy and a decrease in expression of p21, but not CDK2 or p27. Furthermore, apoptosis was not present in PHN, but was increased in rats given bFGF. In conclusion, this study shows that the low proliferative capacity of the GEC in vivo in response to immune injury may be due to an increase in the expression of specific cyclin kinase inhibitors. The increase in mitosis in PHN rats given bFGF may be due to a decrease in p21. Thus, changes in **cell cycle regulatory** proteins may regulate the response of GEC to injury and underlie the development of progressive glomerulosclerosis in diseases of the GEC.

L2 ANSWER 21 OF 28 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 97048442 EMBASE
DOCUMENT NUMBER: 1997048442
TITLE: **Cyclin-dependent kinase** inhibitor expression in pulmonary clara cells transformed with SV40 large T antigen in transgenic mice.
AUTHOR: Magdaleno S.M.; Wang G.; Mireles V.L.; Ray M.K.; Finegold M.J.; DeMayo F.J.
CORPORATE SOURCE: F.J. DeMayo, Department of Cell Biology, Baylor College of Medicine, Houston, TX 77030, United States
SOURCE: Cell Growth and Differentiation, (1997) 8/2 (145-155).
Refs: 32
ISSN: 1044-9523 CODEN: CGDIE7

COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
021 Developmental Biology and Teratology
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Expression of **cell cycle regulatory** genes in mouse lung was investigated in transgenic models for Clara cell transformation. Clara cells were transformed by generating transgenic mice in which the SV40 large T antigen was expressed under the control of the mouse Clara cell M(r) 10,000 protein promoter. The resulting lung tumors express the large T antigen in normal Clara cells and in tumors, and these tumors express reduced levels of CC10 mRNA. The expression of **cell cycle regulatory** protein, p53, and the **cyclin-dependent kinase** inhibitors was analyzed by Northern blot analysis and in situ hybridization throughout the progression of Clara cell transformation in the lung. Increases in specific **cyclin-dependent kinase** inhibitor steady-state mRNA levels were detected in p15, p18, p27, and p57 during tumor progression. The expression of p15, p57, and p21 mRNAs were verified by in situ hybridization. Using this approach, regulatory genes have been identified that may be involved in the regulation of Clara cell differentiation.

L2 ANSWER 22 OF 28 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.DUPLICATE 10
ACCESSION NUMBER: 97165732 EMBASE
DOCUMENT NUMBER: 1997165732
TITLE: **Cell cycle regulatory** proteins - An overview with relevance to oral cancer.
AUTHOR: Goodger N.M.; Gannon J.; Hunt T.; Morgan P.R.
CORPORATE SOURCE: P.R. Morgan, Department Oral Medicine/Pathology, UMDS, *Guy's Campus, Guy's Tower*, London Bridge, London SE1 9RT, United Kingdom
SOURCE: European Journal of Cancer Part B: Oral Oncology, (1997) 33/2 (61-73).
Refs: 246
ISSN: 0964-1955 CODEN: EJCCER
PUBLISHER IDENT.: S 0964-1955(96)00071-1
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
011 Otorhinolaryngology
016 Cancer
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The cell cycle is controlled by a number of highly conserved proteins, found in species as diverse as yeast and mammals. The study of these proteins is a rapidly advancing field that is increasing our understanding of normal and abnormal cell division. Disruption of the cell cycle has been demonstrated in several different types of neoplasm, and there is increasing evidence that, in head and neck tumours, there is aberrant control of cyclins, cell cycle protein kinases and their inhibitors. Because of the phase specificity of some of the control proteins, antibodies to them are proving to be of value in studying cell kinetics of both normal tissues and malignant tumours.

L2 ANSWER 23 OF 28 MEDLINE
ACCESSION NUMBER: 97042011 MEDLINE
DOCUMENT NUMBER: 97042011
TITLE: *Changes in cell-cycle protein expression during* experimental mesangial proliferative glomerulonephritis.
AUTHOR: Shankland S J; Hugo C; Coats S R; Nangaku M; Pichler R H; Gordon K L; Pippin J; Roberts J M; Couser W G; Johnson R J
CORPORATE SOURCE: Division of Nephrology, University of Washington, Seattle, USA.
CONTRACT NUMBER: DK43422 (NIDDK)
DK02142 (NIDDK)
DK47659 (NIDDK)
SOURCE: KIDNEY INTERNATIONAL, (1996 Oct) 50 (4) 1230-9.
Journal code: KVB. ISSN: 0085-2538.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199705
ENTRY WEEK: 19970503
AB A characteristic response to mesangial cell injury is proliferation, which is closely linked to mesangial matrix accumulation and the progression of glomerular disease. Cell proliferation in non-renal cells in vitro is regulated at the level of the cell-cycle by specific cyclins and their catalytic partners, cyclin dependent kinases (CDK). Cyclin kinase inhibitors (CKI) prevent proliferation by inhibiting cell-cycle progression. However, the expression of **cell-cycle regulatory** proteins in the kidney and in renal disease is unknown. To determine this we studied the expression of cell-cycle proteins in vivo in normal rats and rats with experimental mesangial proliferative glomerulonephritis (Thy1 model). Normal quiescent rat glomeruli have a differential expression for CKI's, where p27Kip1 is highly expressed, and the levels for p21 (Cip1, Waf1, Sdi1, Cap20) (p21) are low. The onset of mesangial cell proliferation in Thy1 glomerulonephritis is associated with a reduction in p27Kip1 levels when mesangial cell proliferation is maximal. Mesangial cell proliferation in vivo is also associated with an increase in glomerular expression of cyclin A, and an increase in expression and activity for CDK2. The resolution of mesangial cell proliferation was associated with a return to baseline levels for p27Kip1, while the expression for p21 increased substantially. Furthermore, mesangial cell p21 expression was maintained following the resolution of proliferation. These results provide evidence for a complex interplay of **cell-cycle regulatory** proteins during the glomerular response to injury in vivo. The marked increase in CDK2 expression during mesangial cell proliferation and the sustained increase in p21 expression following the resolution of mesangial cell proliferation suggests that the in vivo expression of certain cell-cycle proteins may differ from that described in non-renal cells in vitro.

L2 ANSWER 24 OF 28 BIOSIS COPYRIGHT 1999 BIOSIS DUPLICATE 11
ACCESSION NUMBER: 1996:526753 BIOSIS
DOCUMENT NUMBER: PREV199699249109
TITLE: Malignant astrocytomas with homozygous CDKN2/p16 gene deletions have higher Ki-67 proliferation indices.
AUTHOR(S): Ono, Yasuhiro; Tamiya, Takashi (1); Ichiakwa, Tomotsugu; Kunishio, Katsuzou; Matsumoto, Kengo; Furuta, Tomohisa; Ohmoto, Takashi; Ueki, Keisuke; Louis, David N.
CORPORATE SOURCE: (1) Dep. Neurological Surgery, Okayama Univ. Med. Sch., 2-5-1 Shikata-cho, Okayama 700 Japan
SOURCE: Journal of Neuropathology & Experimental Neurology, (1996) Vol. 55, No. 10, pp. 1026-1031.
ISSN: 0022-3069.
DOCUMENT TYPE: Article
LANGUAGE: English
AB p16 is involved in a **cell-cycle regulatory** cascade that includes **cyclin-dependent kinase** 4 (cdk4), cyclin D1 and pRb. Alterations of each of these components have been described in primary human glioblastoma multiforme (GBM) or GBM cell lines, and alterations of the individual components of this pathway appear inversely correlated with one another. While this suggests that disruption of any individual component has similar oncogenic effects, homozygous deletions of the CDKN2/p16 gene are the most common genetic alteration. We investigated the relationship between homozygous CDKN21 p16 deletions and cellular proliferation in 50 primary astrocytomas (2 WHO grade I pilocytic astrocytoma, 15 grade II astrocytomas, 20 grade III anaplastic astrocytomas and 13 grade IV GBMs). Using a comparative multiplex PCR assay, homozygous deletions of the CDKN2/p16 gene were detected in 5 anaplastic astrocytomas (25%) and 6 GBMs (46%), but in none of the lower-grade tumors. Ki-67 immunohistochemistry was used to assess the number of proliferating cells in the same samples used for molecular genetic analysis. In both anaplastic astrocytomas and GBMs, Ki-67 proliferation indices were significantly higher in tumors with CDKN2/p16 deletions (20%) than in those without deletions (10%; p=0.0001). These results suggest that homozygous CDKN2/p16 deletions in high-grade astrocytomas may have a more deleterious effect on cell cycle control than the other aberrations in the p16-cdk4-cyclin D1-pRb pathway, and may provide one explanation for why homozygous CDKN2/p16 deletions are more common genetic events in high-grade astrocytomas than RB mutations or CDK4 amplification.

L2 ANSWER 25 OF 28 MEDLINE DUPLICATE 12
ACCESSION NUMBER: 96343851 MEDLINE
DOCUMENT NUMBER: 96343851
TITLE: Induction of **cell cycle regulatory** proteins in anti-immunoglobulin-stimulated mature B lymphocytes.
AUTHOR: Solvason N; Wu W W; Kabra N; Wu X; Lees E; Howard M C
CORPORATE SOURCE: Department of Immunology, DNAX Research Institute, Palo Alto, California 94304-1104, USA.
SOURCE: JOURNAL OF EXPERIMENTAL MEDICINE, (1996 Aug 1) 184 (2) 407-17.
Journal code: I2V. ISSN: 0022-1007.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199611
AB Progression through the cell cycle is a tightly controlled process that integrates signals generated at the plasma membrane with the proteins that form the cell cycle machinery. The current study chronicles the induction of cyclins, cyclin-dependent kinases (**cdk**), and **cdk** inhibitors in low density primary mouse B lymphocytes after anti-immunoglobulin plus interleukin 4 (IgM + IL-4) stimulation. In this system, > 85% of cells remain in the G0/G1 phase of cell cycle for an initial 24-h period, followed by entry of up to 50% of the cells into S phase, commencing around 30 h and peaking at 48 h. Extensive time course analyses of these anti-IgM + IL-4-stimulated B cells revealed that the G1-associated D-type cyclins D2 and D3 were induced by 3 h after

stimulation, and that cyclins E, A, and B were subsequently induced sequentially, beginning at mid-G1, G1/S transition, and S phase, respectively. The G1-associated cyclin D1 was not expressed at any stage of the anti-Ig + IL-4-induced B cell cycle. cdk2, cdk4, and cdk6 were induced during G1, whereas cell division cycle-2 (cdc2) was induced concomitantly with S phase. Irrespective of their expression, the kinases cdk2 and cdc2 were only active from S phase onwards, suggesting that productive cyclin/kinase complex formation did not occur until that time. Cell cycle inhibitors p21 and p19 were induced by anti-Ig + IL-4, peaking in expression at mid-G1 and S phase, respectively. Stimulation of low density B cells with anti-Ig + IL-4 caused rapid down regulation of the p27 inhibitor, however this protein was reexpressed at 54-96 h after stimulation. In contrast, B cells stimulated with anti-CD40, a stimulus which induces long-term B cell proliferation, permanently down regulated p27. These findings are consistent with the concept that p27 reexpression
contributes to the G1 arrest that follows antigen receptor crosslinking. Low density B cells cultured in the viability-enhancing cytokine IL-4 alone also showed induction of D2 and D3 cyclin expression. However, the [redacted]D2 expression was transient, and the D3 expression was substantially [redacted]wer
than that observed in B cells induced to proliferate by anti-Ig + IL-4. This partial induction of D2 and D3 expression may explain IL-4's ability to promote B cell entry into G1 but not S phase of cell cycle, and furthermore, its ability to truncate G1 progression when B cells are subsequently stimulated with anti-Ig.

L2 ANSWER 26 OF 28 MEDLINE DUPLICATE 13
ACCESSION NUMBER: 96407041 MEDLINE
DOCUMENT NUMBER: 96407041
TITLE: Amplification of the cyclin-dependent kinase 4 (CDK4) gene is associated with high cdk4 protein levels in glioblastoma multiforme.
AUTHOR: Rollbrocker B; Waha A; Louis D N; Wiestler O D; von Deimling A
CORPORATE SOURCE: Department of Neuropathology, University of Bonn Medical Center, Germany.
CONTRACT NUMBER: CA57683 (NCI)
SOURCE: ACTA NEUROPATHOLOGICA, (1996 Jul) 92 (1) 70-4. Journal code: ICE. ISSN: 0001-6322.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
Journal; Article; (JOURNAL ARTICLE)
[redacted]NGUAGE: English
[redacted]LE SEGMENT: Priority Journals
ENTRY MONTH: 199705
ENTRY WEEK: 19970502
AB Genetic alterations on the long arm of chromosome 12, including both gene
amplification and allelic loss, are associated with malignant progression of human gliomas. The region of the chromosomal arm 12q that is amplified in malignant gliomas contains the CDK4 gene, a cell cycle regulatory gene which promotes cell division. To evaluate the frequency of CDK4 gene amplification, we analyzed a series of
355 brain tumors using a quantitative non-radioactive polymerase chain reaction assay. CDK4 gene amplification occurred in 9 of 81 glioblastomas (11%), but was rare in other neoplasms, including low-grade and anaplastic gliomas, meningiomas, medulloblastomas and metastatic carcinomas (only 6 of 274 cases). There was no correlation between CDK4 gene amplification and allelic loss of chromosome 12. To assess the significance of CDK4 gene amplification, we analyzed protein extracts from 37 glioblastomas by Western blotting with a commercially available polyclonal antibody to cdk4. All tumors with CDK4 gene amplification showed high cdk4 expression levels, whereas no increased cdk4 expression was seen in glioblastomas without CDK4 gene amplification. These data support the functional activity of CDK4 gene amplification in glioblastoma multiforme and point to an important role of CDK4 gene amplification in a subset of glioblastomas.

L2 ANSWER 27 OF 28 BIOSIS COPYRIGHT 1999 BIOSIS
ACCESSION NUMBER: 1996:16370 BIOSIS
DOCUMENT NUMBER: PREV199698588505
TITLE: Cytokine induction of proliferation and expression of CDC2 and cyclin A in FDC-P1 myeloid hematopoietic progenitor cells: Regulation of ubiquitous and cell cycle-dependent histone gene transcription factors.
AUTHOR(S): Shakoori, A. R.; Van Wijnen, A. J.; Cooper, C.; Aziz, F.; Birnbaum, M.; Reddy, G. P. V.; Grana, X.; De Luca, A.; Giordano, A.; Lian, J. B.; Stein, J. L.; Quesenberry, P.; Stein, G. S.
CORPORATE SOURCE: Dep. Cell Biol. Hematol. Oncol., Univ. Massachusetts Med. Sch. Comprehensive Cancer Cent., 55 Lake Ave. North, Worcester, MA 01655 USA
SOURCE: Journal of Cellular Biochemistry, (1995) Vol. 59, No. 3, pp. 291-302. ISSN: 0730-2312.
DOCUMENT TYPE: Article
LANGUAGE: English
AB To evaluate transcriptional mechanisms during cytokine induction of myeloid progenitor cell proliferation, we examined the expression and activity of transcription factors that control cell cycle-dependent histone genes in interleukin-3 (IL-3)-dependent FDC-P1 cells. Histone genes are transcriptionally upregulated in response to a series of cellular regulatory signals that mediate competency for cell cycle progression at the G1/S-phase transition. We therefore focused on factors
that are functionally related to activity of the principal cell cycle regulatory element of the histone H4 promoter: CDC2, cyclin A, as well as RB- and IRF-related proteins. Comparisons were made with activities of ubiquitous transcription factors that influence a broad spectrum of promoters independent of proliferation or expression of
tissue-specific phenotypic properties. Northern blot analysis indicates that cellular levels of cyclin A and CDC2 mRNAs increase when DNA synthesis and H4 gene expression are initiated, supporting involvement in cell cycle progression. Using gel-shift assays, incorporating factor-specific antibody and oligonucleotide competition controls, we define three sequential periods following cytokine stimulation of FDC-P1 cells when selective upregulation of a subset of transcription factors is observed. In the initial period, the levels of SP1 and HiNF-P are moderately elevated; ATF, AP-1, and HiNF-M/IRF-2 are
maximal during the second period; while E2F and HiNF-D, which contain cyclin A as a component, predominate during the third period, coinciding with maximal H4 gene expression and DNA synthesis. Differential regulation
of H4 gene transcription factors following growth stimulation is consistent with a principal role of histone gene promoter elements in integrating cues from multiple signaling pathways that control cell cycle induction and progression. Regulation of transcription factors controlling histone gene promoter activity within the context of a staged cascade of responsiveness to cyclins and other physiological mediators of proliferation in FDC-P1 cells provides a paradigm for experimentally addressing interdependent cell cycle and cell growth parameters that are operative in hematopoietic stem cells.

L2 ANSWER 28 OF 28 CANCERLIT
ACCESSION NUMBER: 94697521 CANCERLIT
DOCUMENT NUMBER: 94697521
TITLE: Cyclin-dependent kinases and human cell cycle regulation (Meeting abstract).
AUTHOR: Lukas J; Baldin V; Pagano M; Bartek J; Draetta G
CORPORATE SOURCE: European Molecular Biology Lab., Postfach 10 2209, D-6900 Heidelberg, Germany.
SOURCE: Non-serial, (1993). EACR-12, pp. 12th Biennial Meeting of the European Association for Cancer Research. April 4-7, 1993, Brussels, Belgium, 1993. :.
DOCUMENT TYPE: (MEETING ABSTRACTS)
FILE SEGMENT: ICDB; L
LANGUAGE: English
ENTRY MONTH: 199411
AB In mammalian cells, progression through the cell cycle is regulated by a family of protein kinases, the cyclin-dependent kinases. These kinases are inactive as monomers, and require the association with cyclin regulatory subunits for activity. Cyclins control both the activation and the substrate specificity of the catalytic subunit. The cdk complexes are also regulated by phosphorylation. Protein kinases and phosphatases have been identified which, in response to both extracellular
(growth factors, nutrients) and intracellular events, regulate the activation of the cyclin-dependent kinases. The ability to sense changes in the extracellular environment is crucial for the growth homeostasis of a multicellular organism. Most mammalian cells are sensitive to growth factors during the G1 phase of the cell cycle. Upon growth factor deprivation, cells will arrest prior to DNA synthesis. The identification of cell cycle regulatory molecules which are activated in response to growth stimulation in G1 and are themselves responsible for entry into S-phase is therefore of particular interest. A, E and D cyclins are good candidates for such molecules. Cyclins A and E associate with cdk2, forming complexes that are active during late G1 (cyclin E) and during S-phase (both cyclins). Microinjection of antibodies or antisense cDNA to either cyclin A or cdk2 prevents cells from entering S-phase. The cyclin D1 cDNA was cloned through a screen devoted at the identification of genes expressed late in G1 in response to growth stimulation of mouse macrophages with colony-stimulating factor 1. It was also identified for its ability to rescue a yeast strain defective in G1-cyclins. Interestingly, cyclin D1 has also been identified as PRAD1, the product of a gene which is overexpressed in parathyroid adenomas as a result of a genetic rearrangement. Cyclin D1 mRNA and protein are overexpressed in a large fraction of breast carcinomas, esophageal carcinoma, centrocytic lymphomas
and other malignancies. To dissect the role played by cyclin D1, we performed in microinjections of antibodies and antisense plasmids to cyclin D1 in a number of different normal and cancerous cells. Data are presented showing that tumor cells that express cyclin D1 are absolutely dependent on cyclin D1 for progression through the cell cycle. Since cyclin D1 is absent from normal hematopoietic cells, and it drives the cell cycle in some specific tumor tissues, it should be considered as a suitable target for development of specific inhibitors of tumor cell growth.

=> logodd

LOGODD IS NOT A RECOGNIZED COMMAND
The previous command name entered was not recognized by the system. For a list of commands available to you in the current file, enter "HELP COMMANDS" at an arrow prompt (=>).

09/016,869

=> logoff

ALL L# QUERIES AND ANSWER SETS ARE DELETED AT LOGOFF
LOGOFF? (Y)/N/HOLD:y

COST IN U.S. DOLLARS	ENTRY	SINCE FILE SESSION	TOTAL
FULL ESTIMATED COST		34.08	34.53

STN INTERNATIONAL LOGOFF AT 11:19:51 ON 17 SEP 1999